REMARKS

A Petition for Extension of Time is being concurrently filed with this Response. Thus, the Response is being timely filed.

Applicants respectfully request the Examiner to reconsider the present application in view of the following remarks.

Status of the Claims

Upon entry of the present Response, claims 13-23 are currently pending in the present application. The Office Action is Final. Claims 16-19 and 21-23 are withdrawn from further consideration as being directed to a non-elected invention. Claims 13-15 and 20 are presently being examined on the merits. Since no further amendments are presented, no new matter has been added.

Based upon the above considerations, withdrawal of all rejections is respectfully requested.

Issues Under 35 U.S.C. § 103(a), Obviousness

Claims 13-15 and 20 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Scheel-Kruger *et al.*, U.S. Patent No. 6,288,079 B1, (hereinafter the "'079" patent) combined with Berge *et al.*, "*Pharmaceutical Salts*," J. Pharm. Sci., Vol. 66(1), pp. 1-19, (1977) (hereinafter "Berge").

The Examiner asserts that the affidavit under 37 C.F.R. § 1.132 filed on October 10, 2008 (hereinafter "Declaration") is insufficient to overcome the above rejection. The Examiner suggests that a skilled artisan in the chemical or pharmaceutical arts would have envisioned to make the tartrate salt of the claimed compound from the '079 reference with expectation of reasonable success, because there are only a finite number of pharmaceutically acceptable salts disclosed in the '079 patent and the tartrate salts are also the 4th most commonly commercially marketed salts approved by the FDA as seen in Berge.

The Examiner's finding of insufficiency of the data within the Declaration was based largely on the Examiner's interpretation of *Pfizer, Inc. v. Apotex, Inc.*, 82 USPQ 2d. 1321 (Fed. Cir. 2007).

Additionally, the Examiner asserts that the '079 patent (see the '079 patent at column 5, lines 24-34 and column 22, lines 5-44) discusses salts of the active compounds, including tartrate salts, and the compound (1R, 2R, 3S, 5S)-2-methoxymethyl-3-(3,4-dichlorophenyl)-8-azabicyclo[3.2.1]octane. The Examiner relies on the Berge reference for the general knowledge that tartrate salts are commonly (4th most common) used in the pharmaceutical arts. Finally, the Examiner further asserts that due to the common use of tartrate salts (based on Berge), a skilled artisan in the pharmaceutical art would have envisioned making the tartrate salt of the claimed compound from the '079 patent with an expectation of reasonable success. Applicants respectfully traverse.

Applicants again respectfully disagree with the Examiner that the provided Declaration does not show unexpected results. The Declaration indeed shows unexpected results, as shown with the following comments. Applicants have previously provided within the IDS filed January

30, 2006, the article of Keverline-Frantz *et al.*, "*Synthesis and ligand binding of tropane ring analogues of paroxetine*," J. Med. Chem., Vol. 41, No.2, pp 247-297 (1998) (hereinafter "Keverline").

Keverline is directed to tropane compounds, *i.e.*, compounds structurally related to the compounds of the present invention. Keverline discloses the synthesis of a number of the compounds in the experimental part of the document (see Keverline, pages 252-256), which are tartrate salts. Within the descriptions for the compounds, they are characterized as "hygroscopic." The tartrate salt compounds characterized as "hygroscopic" include:

(1R)-3α-(4-Fluorophenyl)-2β-(hydroxymethyl)tropane
3β-(4-Fluorophenyl)-2α-[[3,4-(methylenedioxy)phenoxy]methyl] tropane
3α-(4-Fluorophenyl)-2β-[[3,4-(methylenedioxy)phenoxy]methyl] tropane
(1S)-3β-(4-Fluorophenyl)-2α-[[3,4-(methylenedioxy)phenoxy]methyl] tropane
(1S)-3α-(4-Fluorophenyl)-2β-[[3,4-(methylenedioxy)phenoxy]methyl] tropane
3β-(4-Fluorophenyl)-2β-[[3,4-(methylenedioxy)phenoxy]methyl] nortropane
(1R)-3β-(4-Fluorophenyl)-2α-[[3,4-(methylenedioxy)phenoxy]methyl] nortropane
(1R)-3α-(4-Fluorophenyl)-2β-[[3,4-(methylenedioxy)phenoxy]methyl] nortropane
(1S)-3β-(4-Fluorophenyl)-2β-[[3,4-(methylenedioxy)phenoxy]methyl] nortropane
(1S)-3β-(4-Fluorophenyl)-2α-[[3,4-(methylenedioxy)phenoxy]methyl] nortropane, and
(1S)-3α-(4-Fluorophenyl)-2β-[[3,4-(methylenedioxy)phenoxy]methyl] nortropane.

Hence, based on Keverline, Applicants submit that it is surprising and one skilled in the art would neither predict nor expect that the tartrate salt compounds of the present application would, in fact, be very non-hygroscopic in view of the teachings within Keverline.

With regards to *Pfizer, Inc. v. Apotex, Inc.*, *supra*, when discussing "Motivation to combine prior art" on page 1332, first full paragraph, it is stated that

> *"...out of the list of 53 anions, one of ordinary skill in the art would have favorably considered benzene sulphonate because of its known acid strength, solubility and other known chemical characteristics as reported in several other publications Pfizer has admitted are prior art. Schmidt discloses that aryl sulphonic acids, such as benzene sulphonic acids, considerably increase the solubility of pharmaceuticals containing one or more basically reacting nitrogen*

atoms. '612 patent col. 2 11.14-41. Spiegel specifically identifies besylate as the preferred pharmaceutically-acceptable acid addition salt form of a pharmaceutical compound. '637 patent col. 2 11.38-39. Other patent not before the examiner during prosecution of the '303 patent also point to benzene sulphonate. U.S. Patent 3,970,662 to Carabateas (1976) discloses an intermediate dihydropyridine compound useful in the form of an acid addition salt derived from benzene sulphonate. '662 patent cal. 3 11.35-49 & col. 4 11.20-24. U.S. Patent 4,432,987 to Barth (1984), assigned to Pfizer, discloses the besylate acid addition salt form of a pharmaceutical composition having excellent pharmacokinetic properties, near-optimal solubility, and improved stability. '987 patent col.2 1145-46. Taken together, these references provide ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate."

With regards to the discussion of "obvious-to-try" within *Pfizer, Inc. v. Apotex, Inc.*, *supra*, on page 1334, fifth full paragraph, it is stated that:

"First, this is not the case where there are "numerous parameters" to try. Rather, the only parameter to be varied is the anion with which to make the amlodipine acid addition salt. Although we recognize some degree of unpredictability of salt formation,...the mere possibility that some salts may not form does not demand a conclusion that those that do are necessarily non-obvious. This is especially true here where (1) as noted above, the skilled artisan had a reasonable (although not guaranteed) expectation that amlodipine besylate would form; (2) Pfizer conceded in prior ligation that the type of salt had no effect on the therapeutic effect of the active ingredient, amlodipine, and was practically interchangeable,...and (3) numerous other publications (described above) clearly directed the skilled artisan to a pharmaceutically-acceptable acid addition salt made from benzene sulphonate, including, significantly, the Carabateas patent which taught the besylate acid addition salt form of another dihydropyridine pharmaceutical compound."

Further in *Pfizer, Inc. v. Apotex, Inc.*, *supra*, the sixth full paragraph on page 1334 states that:

"Second this is not the case where the prior art teaches merely to pursue a "general approach that seemed to be a promising field of experimentation" or "gave only general guidance as to the particular form of the claimed invention or how to achieve it"...[I]n selecting an acid addition salt formulation, one skilled in the art looked to pharmacopoeias and compendia to find a salt that was previously approved by the FDA and used successfully within the pharmaceutical industry. Berge clearly pointed the skilled artisan to 53 anions that as of 1974, were pharmaceutical acceptable. As Dr. Wells' testimony and the Carabateas patent demonstrated, one of ordinary skill in the art was capable of further

narrowing that list of 53 anions to a much smaller group, including benzene sulphonate, with a reasonable expectation of success."

Applicants submit that the present application differs from the case within *Pfizer, Inc. v. Apotex, Inc., supra*, in at least two ways.

Firstly, in order to distinguish the findings within *Pfizer, Inc. v. Apotex, Inc., supra,* Applicants bring to the Examiner's attention *Sanofi-Synthelabo v. Apotex Inc.*, 89 USPQ2d 1370 (Fed. Cir. 2008). Particularly, Applicants submit that on page 1379, the court's conclusions provide further support to Applicants' arguments:

> *...Concerning the bisulfate salt, the district court found no evidentiary support for Apotex's argument that the '596 patent taught the dextrorotatory enantiomer of PCR 4099 as the bisulfate salt. The PCR 4099 racemate is shown in the '596 patent as the hydrochloride, not the bisulfate. The district court observed that the scientific literature listed eighty acids as candidates for forming salts with basic drug compounds, fifty-three of which acids had been used in FDA-approved drugs. The experts of both parties agreed that whether a pharmaceutically suitable crystalline salt will form from a particular acid-base combination is unpredictable. The district court distinguished the facts of this case from those of Pfizer 480 F.3d 1348, where there was evidence that based on the prior art a person of ordinary skill would have narrowed the possible salts to only a few including the claimed besylate, whereas here Sanofi presented evidence that the prior art taught away from the use of sulfuric acid with an enantiomer, for strong acids could encourage re-racemization....* Sanofi-Synthelabo v. Apotex Inc., 89 USPQ2d 1370, 1379 (Fed. Cir. 2008). (emphasis added).

Although the Examiner asserts that the skilled artisan would envision making the tartrate salt of the '079 patent, since there is only a finite number of acceptable salts within the '079 patent and a tartrate salt is the fourth most commercially marketed salts approved by the FDA, Applicants respectfully submit that based on Keverline and *Sanofi-Synthelabo v. Apotex Inc., supra*, the Examiner's premise is incorrect.

Specifically, the prior art cited by the Examiner is silent with regards to the hygroscopicity of the citrate and the tartrate salts as well as any other acid salt. The two documents cited by the Examiner do not clearly direct the skilled artisan to the tartrate salt. Further, Applicants submit that the teachings within the documents do not suggest or motivate the skilled person to select the tartrate salt.

In fact, based on what was known in the art regarding tartrate salts, one skilled in the art would not be led in the direction of tartrate salts. Keverline indicates that tartrate salts that are similar to the tropane compounds of the present invention are mostly hygroscopic. Applicants have distinguished the facts of the present application from those of *Pfizer, Inc. v. Apotex, Inc.*, 82 USPQ 2d. 1321 (Fed. Cir. 2007). Applicants provided evidence within the Declaration that runs counter to the prior art teaching in Keverline. Keverline teaches that tartrate salts similar to the compounds in the present invention are predominantly hygroscopic. Applicants' submitted Declaration provides evidence that the tropane compounds of the present invention are <u>not hygroscopic</u>.

Applicants further submit that the Examiner's premise that the skilled artisan would select a tartrate salt is also incorrect. Based on the Keverline reference, a skilled artisan would predict that for tropane compounds, a pharmaceutically suitable crystalline tartrate salt will mostly be hygroscopic and therefore it is unpredictable to assume that it would be a proper salt for tropane compounds. Keverline teaches away from the use of a tartrate salt since similar tropane tartrate salt compounds were shown to be hygroscopic. Additionally, Applicants submit that the provided Declaration is sufficient to overcome the rejection since it shows unexpected advantageous results.

Secondly, in the '079 patent, a group of pharmaceutically acceptable salts is mentioned (see the '079 patent at column 5, lines 24-33). This group amounts to 27 different salts and includes:

> Hydrochloride, hydrobromide, phosphate, nitrate, perchlorate, sulphate, citrate, lactate, tartrate, maleate, fumarate, mandelate, benzoate, ascorbate, cinnamate, benzenesulfonate, methanesulfonate, stearate, succinate, glutamate, glycollate, toluene-p-sulphonate, formate, malonate, naphthalene-2-sulphonate, salicylate, and acetate.

In the above list of salts, 9 specific salts, which are underlined, cannot be found in Table I of the Berge reference. Hence, Applicants also submit that in order to arrive at the invention in the present case, the skilled artisan is first pointed in the direction of the 53 anions listed in the Berge document. Additionally, when combining the teaching of Berge with the teaching of '079 patent, this list is further expanded by including the additional 9 salts of the '079 patent. Finally, the skilled artisan must select the tartrate salt among these 62 salts. However, as pointed out above, the teachings of Keverline indicate tartrate compounds that are similar are unsuitably hygroscopic. Applicants respectfully submit that for a skilled artisan concerned about hygroscopic properties, Keverline teaches away from using tartrate salts for tropane compounds.

As in *Sanofi-Synthelabo v. Apotex Inc.*, *supra*, Applicants have provided evidence within the Keverline reference that the prior art taught away from the use of tartrate salts for tropane compounds, because tartrate salts encourage undesirable hygroscopic properties. Further Applicants provided a Declaration that shows that the tartrate salt compounds of the present invention are non-hygroscopic, which is an unexpected result based on the prior art. Therefore, Applicants respectfully submit that the submitted Declaration is sufficient to overcome the rejections alleged by the Examiner.

As Applicants pointed out previously and in lieu of the above, Applicants respectfully submit that the Examiner has not appropriately resolved the factors spelled out in *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), including the factors of determining the scope and content of the prior art, ascertaining the differences between the prior art and the claims that are at issue and evaluating any evidence of secondary considerations. Based on the above, Applicants maintain that the above mentioned *Graham* factors actually reside in Applicants' favor, especially ascertaining the differences between the prior art and the claims that are at issue and evaluating any evidence of secondary considerations (e.g., commercial success; unexpected results). *Graham v. John Deere*, 383 U.S. at 17, 148 USPQ at 467. Additionally, Applicants submit that since the Examiner did not resolve the *Graham* factors, the rationale the Examiner provides based on M.P.E.P. § 2143 for combining the cited references is improper. To reject a claim based on the above mentioned rationale, the Examiner must resolve the *Graham* factual inquiries. MPEP §2143.

Applicants respectfully submit that the presently claimed invention is distinct from and unobvious over the '079 patent combined with Berge.

In light of the above remarks, because there is no disclosure, teaching, suggestion, reason or rationale provided in the cited references that would allow one of ordinary skill in the art to arrive at the instant invention as claimed, it follows that the same references are incapable of rendering the instant invention obvious under the provisions of 35 USC § 103(a). Based upon the above, and applying the *Graham factors* analysis test, it is submitted that a *prima facie* case of obviousness has not been established.

Applicants respectfully request reconsideration and subsequent withdrawal of the above rejections.

CONCLUSION

A full and complete response has been made to all issues as cited in the Office Action. Applicants have taken substantial steps in efforts to advance prosecution of the present application. Thus, Applicants respectfully request that a timely Notice of Allowance issue for the present case.

In view of the above remarks, it is believed that claims are allowable.

Should there be any outstanding matters within the present application that need to be resolved, the Examiner is respectfully requested to contact Paul D. Pyla, Reg. No. 59,228, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____

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